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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/895,141	06/29/2001	Seymour Benzer	30431.3US01	8276

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EXAMINER	
MCGILLEM, LAURA L	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 10/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/895,141	BENZER ET AL.	
	Examiner	Art Unit	
	Laura McGillem	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

It is noted that the petition under 37 CFR 1.181, filed 2/8/2005 for withdrawal of abandonment based on premature abandonment has been granted in the Petition decision of 4/29/2005. Further, the notice that the amendment (filed 4/19/2004) presenting claims 33-43 were non- responsive, has been found to be in error and is withdrawn.

Claims 1-32 have been canceled. Claims 33-43 are under examination.

Priority

It is noted that this Application receives priority benefit of Provisional Application No. 60/215,401.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: Inventor Kyung-Tai Min did not sign the oath.

Specification

The disclosure is objected to because of the following informalities:

Applicants have submitted SEQ ID NOs 1-54, but none of them are mentioned in the specification. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33 is vague and indefinite because it recites the phrase "increase activity of at least one gene" and it is not clear to what the activity of the gene is being compared so that the skilled artisan would know if the activity had been increased in order to meet the limitation of the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increasing the life span of *Drosophila* and yeast, does not reasonably provide enablement for extending the life span of all organisms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Applicants claim a method for extending the life span of an organism comprising administering a histone deacetylase inhibitor in an amount effective to increase activity

of at least one gene encoding a protein selected from superoxide dismutase, cytochrome P450 or glutathione transferase to extend the lifespan of the organism.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation *United States v. Telectronics*, Inc., 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

1) Scope of the claims. The scope of the claims encompasses increasing activity of superoxide dismutase, cytochrome P450 or glutathione S transferase gene by inhibiting histone deacetylase to increase the life span of an organism. The specification contemplates invertebrate organisms (including insects and nematodes) and vertebrate organisms (including amphibians, murines, avians, canines, felines, porcines, equines, bovines and humans), which encompasses an incredibly large and diverse group of organisms to have an increased life span. Each of these types of organism has a very different life span (*Drosophila* versus human, for example).

2) State of the Art. Zou et al (2000, of record) teach that aging is a universal biological process which is poorly understood and under intensive study. Zou et al teach that analysis of yeast, nematode, fly and mouse have uncovered several genes that may increase the lifespans of these organisms including superoxide dismutase and methuselah (see page 13726, left column). Zou et al teach that the aging process for

Drosophila is accompanied by a reduction in expression of genes involved in reproduction metabolism and protein turnover. Zou et al teach that more than 60% of age-regulated genes show little response to oxidative stress. Zou et al also teach that a comparison of their results with those of a similar study in mouse revealed no genes that were regulated in the same direction in aging of flies or mouse. Zou et al teach that genes that serve as markers may encode causal factors in aging or may merely reflect changes as a result of aging. Zou et al conclude that the characterization of gene expression changes does not allow distinction between these two types of genes (see page 13731, for example).

3) Unpredictability of the art. In the response filed 4/19/2004, Applicants submit that *Drosophila* is currently accepted by the scientific community as a model system that is predictive of outcomes in other organisms. Applicants cite Reiter et al to show that *Drosophila* is an accepted model organism for the study of disease in other organisms. Reiter et al teach the comparison of known human disease-associated genes from the OMIM database to the *Drosophila* genome sequence to create a database of *Drosophila* genes that are related to candidate human disease genes. Reiter et al teach that the function of endogenous *Drosophila* gene human disease counterparts can be analyzed by loss-of-function and gain-of-function studies in *Drosophila*. However, Reiter et al also teach that some genes common to *Drosophila* and human may not be performing equivalent functions in the two organisms, since some *Drosophila* systems are relatively simpler than those of humans (see page 1122, right column, 2nd paragraph). Reiter et al teach that another limitation of comparison of

human disease genes and *Drosophila* genes is that some of the related *Drosophila* genes may not be functionally equivalent to the human disease genes, but instead related by sequence and activity to another human gene that has a different function than the human disease gene. The gene may be a member of related but functionally diverged gene family. Therefore, while *Drosophila* is a useful model system to analyze gene function in various disorders by examining mutations or deletions, it is unpredictable whether all gene studies in *Drosophila* will be applicable to the human.

Applicants submit that there is no reason to believe that the exemplified method in *Drosophila* would not similarly be effective with respect to other types of organisms. Applicants cite Lea et al (of record) as describing use of 4-phenylbutyric acid (PBA) and structural analogs, to effectively inhibit histone deacetylase in several different cell types, as well producing the similar downstream effect of inhibiting cell growth. For example, Lea et al reported that PBA and structural analogs inhibited histone deacetylase in both mouse erythroleukemia cells and human leukemic cells, thereby inhibiting growth of these cells. Applicants submit that the results reported by Lea et al confirm that agents that inhibit histone deacetylase effectively decrease histone acetylation in multiple cell types and produce downstream effects similar to those reported for PBA in the cells of various organisms. Applicants submit that those of skill in the art would know how to contact an organism with an inhibitor of histone deacetylase to increase activity of genes associated with free radical resistance such as superoxide dismutase, cytochrome P450, and glutathione S transferase (GST).

The unpredictability of being able to increase the gene activity of GST, cytochrome P450 or superoxide dismutase and extend the life span of an organism is manifested in the multiple factors involved in life span and the complexity of the aging process. Although administration of a histone deacetylase inhibition may induce histone acetylation in cells as exemplified by Lea et al, inhibition of growth of a few cultured cell types does not directly translate to extension of the life span of an entire organism. The effect that increasing activity of said genes would extend the natural lifespan of an organism is unpredictable given the complexity of the metabolism of any vertebrate organism. Therefore, it is unpredictable whether the increase in gene activity of GST, cytochrome P450 or superoxide dismutase that extended the life span of flies would have a similar effect in other organisms. In addition, Orr and Sohal (1993, of record) found that overexpression of superoxide dismutase in *Drosophila melanogaster* has either a minor or insignificant effect on fly life span (see page 34, abstract, for example) and no detectable effect on the maximum life span (see page 39, right column). However, Orr and Sohal (1994, of record) later teach that overexpression of superoxide dismutase in combination with catalase does extend life span (see page 263, center column), suggesting that aging mechanisms are complex. Although the skilled artisan would be able to contact an organism with some amount of an inhibitor of histone deacetylase, such as butyric acid, to increase activity of genes associated with free radical resistance selected from superoxide dismutase, cytochrome P450, and glutathione S transferase, it is unpredictable whether this effect would increase the life span of any organism.

4) Amount of guidance provided. Applicants submit that undue experimentation would not be required for one skilled in the art to practice the invention, using the guidelines and procedures presented in the specification to extend the life span of various types of cells and other organisms. The instant claims are drawn to a method of extending life span, which equates with treating or preventing aging. The specification discloses a variety of conventional methods of administration of the butyric acid derivatives in a variety of conventional forms. The specification discloses that the dosage regimen is dependent on the subject's health, response to treatment and type of subject (see paragraphs 0057-0061). The specification does not give any specific information regarding dosage, treatment regimen, method of administration and number of times the treatment must be administered for any of the contemplated organism beyond *Drosophila*. The specification contemplates but does not provide guidance on what the minimum period of treatment of a histone deacetylase inhibitor will be required in order to extend the life span in any organism. The specification does not provide guidance on how long the gene activity of GST, cytochrome P450 or superoxide dismutase would need to be increased in order to extend the life span of an organism. Although the specification exemplifies that variation of the time points of administration of PBA does not affect the outcome, such that PBA can be administered to a *Drosophila* early or late in life, the specification does not provide guidance on the effect of increased GST, cytochrome P450 or superoxide dismutase gene activity on developing vertebrate organisms, such as human infants or children. Many of the contemplated subject organisms have a significantly longer lifespan than that of a fruit fly. The

specification does not provide guidance regarding whether the histone deacetylase inhibitor should be given to children or instead should be administered to the elderly.

The groups of factors that affect the life span of an organism are incredibly large. Applicants disclose that caloric intake effects life span in rodents, worms and yeast. The specification does not provide any guidance regarding factors such as caloric intake, age, previous health conditions, lifestyle, type of employment, genetic factors, etcetera, besides an increase in gene activity of GST, cytochrome P450 or superoxide dismutase that would effect life span of any organism. The method is not specifically disclosed so that the skilled artisan has been sufficiently informed how to use the claimed method. As *In re Gardner, Roe and Willey*, 427 F.2d 786,789 (C.C.P.A. 1970), there is some possibility that the skilled artisan might eventually find out how to use the invention after "a great deal of work". In the case of *In re Gardner, Roe and Willey*, the inventive compound was not enabled because the inventor failed to disclose how to use the invention based on insufficient disclosure of effective drug dosage. The court held that "the law requires that the disclosure in the application shall inform them how to use, not how to find out how to use for themselves".

5) Working examples. Applicants have provided one example of administering PBA, a histone deactylase inhibitor, to *Drosophila melanogaster* strain w^{118} at various time points in the life span, which appeared to extend median and maximum life span compared to *Drosophila* that had not had PBA. Applicants do not exemplify the use of any other of the claimed histone deactylase inhibitors. Applicants exemplify that expansion of the *Drosophila* life span does not seem to depend on when the PBA is

administered to the flies, either early or late in life. Applicants exemplify significant enhancement of the climbing abilities (locomotor activity) of older *Drosophila* that had been given PBA. Applicants exemplify apparent resistance to the effects of a free radical generator (paraquat) in flies that were given PBA compared to controls. Applicants exemplify apparent resistance to the effects of starvation in flies that were given PBA compared to controls. Applicants demonstrate that flies treated with PBA show an increase in acetylated histones suggesting that regulation of transcription may have been altered compared to untreated flies. Applicants disclose that superoxide dismutase, cytochrome P450 and glutathione S transferase genes are involved in longevity and detoxification, one of the determinant of aging. Applicants demonstrate that each of these genes are induced by PBA treatment.

6) Nature of the invention. The inventive method is drawn inhibiting one enzyme in order to increase activity of other protein to extend the life span of an organism, which are extremely complex and unpredictable aspects of molecular biology and medicine.

7) Level of skill in the art. The level of skill in the art is high, but given the broad scope of the claims, the nature of the invention, level of unpredictability, lack of guidance and the limited scope of the working examples, the skilled artisan would have had to practice an excessive amount of trial and error experimentation in order to practice the claimed method. Given the above analysis of the factors which the Courts have determined are critical in ascertaining whether a claimed invention is enabled, it

must be considered that the skilled artisan would have had to have practiced undue and excessive experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 33-34 and 36-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Nudelman et al (of record).

It is noted that the claims do not recite how long the life span of an organism must be extended to meet the limitation of the claim. The claims do not specify a function for the increased activity of a superoxide dismutase gene, cytochrome P450 gene or glutathione S transferase gene in extending the lifespan of an organism.

Nudelman et al teach the administration of butyric acid and butyric acid derivatives to a B16F0 melanoma primary cancer model. Nudelman et al teach that butyric acid derivatives (pivaloyloxy)methyl butyrate (compound 1a) displayed antitumor

activity that was manifested by a significant increase in the life span of treated animals (see page 687, abstract, for example). Nudelman et al teach that compound 1a brought about a rapid 90% inhibition of *in vitro* cell proliferation, while other butyric acid derivatives showed a maximum of 35% inhibition of proliferation (see page 689, right column, for example). Nudelman et al teach that compound 1a was solubilized in PBS-propylene glycol and administered to a mouse model of B16F0 melanoma for nine days. Nudelman et al teach that treated animals displayed an increased mean survival time, which indicates a significant increase in the life span in the treated animals (see page 691, right column, in particular), which reads on a method for extending the life span of an organism comprising administering an inhibitor of histone deactylase to a subject, wherein the inhibitor of histone deactylase is a soluble butyric acid derivative.

In the response filed 4/19/2004, Applicants submit that Nudelman et al do not teach a method of extending a life span of an organism by administration of a histone deacetylase inhibitor to increase activity of gene encoding superoxide dismutase, cytochrome P450 or glutathione S transferase. However, the life span of the organism was extended by the method taught by Nudelman et al. Absent evidence to the contrary, the (pivaloyloxy)methyl butyrate (compound 1a) was administered in an amount effective to increase activity of at least one superoxide dismutase gene, cytochrome P450 gene or glutathione S transferase gene.

Claims 33-38 are rejected under 35 U.S.C. 102(a) as being anticipated by Repaeli (U.S. Patent No. 5,939,455, 8/17/1999).

It is noted that the claims do not recite how long the life span of an organism must be extended to meet the limitation of the claim or limit the health condition of the organism. The claims do not specify a function for the increased activity of a superoxide dismutase gene, cytochrome P450 gene or glutathione S transferase gene in extending the lifespan of an organism.

Repaeli teaches that compounds can be administered to assess their ability to increase the life span of animals with B16 melanomas compared to untreated animals (see column 14, lines 37-50, for example). Repaeli teaches that compounds can be sodium, arginine and lysine salts of butyric acid, and the butyric acid derivatives isobutyramide, monobutyrin, tributyrin, 2-phenylbutyric acid, 3-phenylbutyric acid 4-phenylbutyric acid, phenylacetic acid, cinnamic acid, alpha-methyldihydrocinnamic acid and 3-chloropropionic acid and 4-phenylbutyric acid in an amount effective to inhibit histone deacetylase in the subject (see column 10, lines 17-45, in particular) which reads on a method to extend the lifespan of an organism by administering an inhibitor of histone deacetylase in an effective amount. Absent evidence to the contrary, since the life span of the organism was extended, the inhibitor of histone deacetylase was administered in an amount effective to increase activity of at least one superoxide dismutase gene, cytochrome P450 gene or glutathione S transferase gene.

Claims 33-38 rejected under 35 U.S.C. 102(e) as being anticipated by Repaeli (U.S. Patent No. 5,939,455, filed 3/11/1997). The teachings of Repaeli are discussed in the above rejection.

Claims 33-37 are rejected under 35 U.S.C. 102(a) as being anticipated by Nudelman et al (U.S. Patent No. 6,030,961, 2/29/2000).

It is noted that the claims do not recite how long the life span of an organism must be extended to meet the limitation of the claim or limit the health condition of the organism. The claims do not specify a function for the increased activity of a superoxide dismutase gene, cytochrome P450 gene or glutathione S transferase gene in extending the lifespan of an organism.

Nudelman et al teach that butyric acid and its sodium salt, sodium butyrate is an inhibitor of nuclear deacetylase, which results in the hyperacetylation of histones. Nudelman et al teach that increased histone treatment as a result of butyric acid treatment is linked to changes in transcriptional activity and the differentiation state of cells (see column 1, lines 21-45, for example). Nudelman et al teach that tributyrin is an analogue of butyric acid (see column 2, lines 38-45, for example). Nudelman et al teach that the butyric acid analogs are advantageous because of their increased water solubility (see column 3, lines 32-35, for example), which reads on the claimed method wherein the butyric acid derivative is soluble and a salt. Nudelman et al teach that therapeutically effective amounts of butyric acid can be used to inhibit histone deacetylase (see column 10, lines 24-45, for example). Nudelman et al teach methods to examine compounds for their ability to increase the life span of animals bearing B16 melanomas, carcinomas and leukemias. Increased survival of the treated animals relative to control animals is an indication of the efficacy of the compounds (see column

14, lines 15-45, for example). Absent evidence to the contrary, since the life span of the organism was extended, the inhibitor of histone deacetylase was administered in an amount effective to increase activity of at least one superoxide dismutase gene, cytochrome P450 gene or glutathione S transferase gene.

Claims 33-37 are rejected under 35 U.S.C. 102(e) as being anticipated by Nudelman et al (U.S. Patent No. 6,030,961, filed 3/1/1997). The teachings of Nudelman et al are discussed in the above rejection.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura McGillem, PhD
9/26/2006

DANIEL M. SULLIVAN
PATENT EXAMINER